REMARKS/ARGUMENTS

The invention

This invention provides for an anti-allergy peptide comprising a cell-penetrating peptide [CPP] from Kaposi fibroblast growth factor fused to either of two specific inhibitors of mast cell activation, $G\alpha t$ or $G\alpha i_3$. In a test of four different CPPs, the claimed CPP from Kaposi fibroblast growth factor was surprisingly discovered to be the *only* CPP able to transport its inhibitor domains in a manner that **inhibited** mast cell activation.

Status of the pending claims

Claims 44, 46, 52-56, 59, 60, 63-70 and 72-79 were pending. Claim 80 was canceled because it was redundant.

Examiner Interview

Pursuant to Rule 133(b), applicants acknowledge the interviews of January 29 and 31, and February 16, with Examiners Crowder and Chan. The interviews were initiated because of the now vacated final Office Action dated December 12, 2006. During the interview, applicants' attorney requested clarification of the Examiner's position with regard to the rebuttal evidence for the *prima facie* case of obviousness. Examiner Crowder vacated the final Office Action and clarified her position in a second final Office Action mailed on March 1, 2007. Although no agreement was reached with regards to the claims, applicants are grateful for the clarification.

35 U.S.C. §103

Holgate in view of Aridor and Lin

The Examiner has maintained her rejection of the pending claims as obvious over Holgate in view of Aridor and Lin. Holgate is relied upon as generally teaching that pharmacological agents can inhibit mast cell degranulation and these agents are useful for

treating diseases such as asthma. Aridor teaches Seq. No. 1 (KNNLKECGLY) and Lin teaches the CPP (AAVALLPAVLLALLAP).

The Examiner presents the *prima facie* case of obviousness by arguing that she has identified the salient elements of the claims, a motivation to combine the elements, and a reasonable expectation that once combined, the recited elements would function to inhibit histamine release by mast cells.

1. THE LAW

A *prima facie* case of obviousness requires the PTO to identify the salient elements of the claim, provide objective reasons for combining the elements and a reasonable expectation that once combined the elements will perform as intended. A *prima facie* case of obviousness is rebuttable. This means that if the applicants believe that any of the three elements are not set forth, the applicants may argue that the *prima facie* case of obviousness is not legally sufficient.

But if a *prima facie* case of obviousness is legally set forth, an obviousness rejection may be overcome (traversed) by a showing that the claimed invention yields unexpected and advantageous results. See, e.g., In re Soni, 54 F.3d 746, 749, 34 U.S.P.Q.2d 1684, 1687 (Fed. Cir. 1995).

> One way for a patent applicant to rebut a prima facie case of obviousness is to make a showing of 'unexpected results,' i.e., to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected.

2. SUMMARY OF PAST ARGUMENTS

In the previous Response, applicants urged that their experimental results as provided in the specification, and the results reported by Jones *et al.,* fully *rebutted* the *prima facie* case of obviousness because only one of four cell-penetrating proteins [CPP] tested

successfully delivered the two mast cell inhibitors so that they inhibited mast cell secretion. This rebuttal argument was based upon an unexpected results position.

The Examiner maintained the obviousness rejection, and applicants now supply two Rule 132 declarations to state for the record that the results set forth in the specification are unexpected, surprising and advantageous. The two declarations are a classic traversal of a *prima facie* case of obviousness.

Applicants believe that the experimental record with Jones is previously sufficient to **rebut** the *prima facie* case of obviousness, and with the submission of the two Rule 132 Declarations, there is now adequate evidence to conclude that the *prima facie* case of obviousness has also been **traversed**.

3. REBUTTAL OF THE *PRIMA FACIE* CASE OF OBVIOUSNESS

In the previous Response, applicants restated their experimental results in the following table:

	CHIMERIC PEPTIDE		RESULTS
Hu Int	$G\alpha i_3$	SEQ ID NO: 6	No inhibition of histamine secretion
KFGF	$G\alpha i_3$	SEQ ID NO: 7	**Inhibited histamine secretion**
Dros	$G\alpha i_3$	SEQ ID NO: 10	Induced histamine secretion
Hu Int	$G\alpha t$	SEQ ID NO: 11	No inhibition of histamine secretion
KFGF SEQ ID NO: 3	$G\alpha t$	SEQ ID NO: 12	**Inhibited histamine secretion**
Dros	$G\alpha t$	SEQ ID NO: 13	Induced histamine secretion
TP-10	$G\alpha i_3$	Jones *et al.*	Induced histamine secretion

As explained previously, the applicants' results, and the confirming prior art of Jones *et al.*, make clear that there is no *a priori* expectation that a particular CPP can both: a)

transport $G\alpha i_3$ and $G\alpha t$ peptides; ***and***, b) retain their inhibitory effects on mast cell degranulation. For this reason, the *prima facie* case of obviousness is fully rebutted.

The Examiner was then asked to articulate objective reasons to support her conclusion that the field is predictable. For without objective reasoning, the §103 based-rejection of the pending claims must be withdrawn.

On page 4 of the outstanding Office Action, the Examiner presents her two objective reasons explaining why the §103 rejection was maintained over the experimental data set forth above.

The Examiner writes on page 5:

Given that the claimed CPP peptide and the mass cell inhibitory peptide are known,

"it is predictable and expected that the AAVALLPAVLLALLAP would be able to transport peptides such as KNNLKECGLY and retain their biological activities"

Applicants agree that "penetration and function" would have been reasonably expected if all one had to read were Holgate, Lin and Aridor. However, the **experimental data in the specification and the Jones publication** cannot be ignored by the Examiner. Clearly, both the table generated from the data in the specification and the results reported in the Jones paper demonstrate that any conclusion regarding expectation of success arising from just reading Holgate, Lin and Aridor is simply wrong. Only penetration of cargo can be expected when using the class of proteins known as CPPs. However, the functionality of the CPP-fused cargo peptides, $G\alpha t$ or $G\alpha i_3$, to inhibit mast cell secretion is unpredictable.

On page 5, the Examiner states that the mechanism of action does not have a bearing on the patentability of the invention if the invention was already known and obvious. The Examiner then goes on to say that the functional results of Jones with CPP, TP-10 from *drosopholia*, were unpredictable in that the expected mast cell inhibition was not detected; but then maintains that Jones is not sufficient to rebut the *prima facie* case of obviousness because,

> In fact, Jones et al., teach that the delivery of peptide cargoes using CPP is a valid method for studying and modulating signal transduction pathways (e.g. see page 207, in particular).

In response, applicants agree with the Examiner's initial position that knowledge of the mechanism of action does not necessarily render an obvious invention patentable. Applicants also agree that the Jones results with TP-10 being the opposite of that which was expected was unpredictable. But applicants strongly disagree that the Examiner's reasoning supports her legal conclusion. Her conclusion is based on two irrelevant truths.

First, the fact that our patent laws tell us that discovery of a "mechanism of action" cannot support an otherwise unpatentable invention is irrelevant to the pending claims because the inventive feature of the pending claims is not based upon a mechanism of action. As stated above, this invention is based on the fact that one cannot predict the biological results of attaching a CPP to a mast cell inhibiting cargo peptide. Rebuttal or traversal of a *prima facie* case of obviousness based on unpredictable results/no expectation of success, has nothing to do with the patent law relating to "mechanism of action."

Second, the fact that Jones tells us that "CPP is a valid method for studying and modulating signal transduction pathways," is another irrelevant truth. The relevant fact is that even Jones could not *a priori* predict what type of modulating would occur with $G\alpha t$ or $G\alpha i_3$ once fused to a CPP. As Jones reported, the TP-10 $G\alpha i_3$ fusion **induced** mast cell secretion instead of inhibiting release. This was the opposite of the expected results, i.e., inhibition type modulation. In the quotation relied upon by the Examiner from page 207, Jones is simply saying that CPP directed protein:protein modulation occurs, but the statement is silent on whether functionality or type of modulation is predictable and the Jones data tells us functionality is not predictable.

And it is in the unpredictability of the results that the subject invention finds its patentability. The fact that the modulation is reproducible is important truth; but, it is an

irrelevant fact with regard to applicants' rebuttal argument because the patentability of the invention is based on the fact that the *type* of modulation is unpredictable.

The Examiner concludes on page 4 of the Office Action with a statement that the references need to be looked at as a combination and not individually; that taken together, the combination of Lin, Aridor and Holgate give rise to a "reasonable" expectation of success.

Applicants agree with the Examiner that Lin, Aridor and Holgate alone would have set forth a proper *prima facie* case of obviousness in the absence of the data set forth in the specification and the Jones *et al.* reference. But that data in the specification and the Jones publication cannot be ignored. In combination, the record clearly establishes that there is more to the story than Lin, Aridor and Holgate would lead one to conclude. We have the applicants' own work, as well as the work of Jones, clearly establishing that penetration by CPP is predictable; but, the functionality of the mast cell inhibiting peptides, $G\alpha t$ or $G\alpha i_3$, after CPP directed penetration into mast cells is not predictable and Lin, Holgate and Aridor do not say otherwise.

The Examiner has never acknowledged the unpredictable results of the applicants and of Jones in her reweighing of the *prima facie* case of obviousness. She has steadfastly relied solely on the three references that made up the original *prima facie* case of obviousness. But the law clearly tells us that patent examiners cannot ignore references that teach away from their original conclusion of obviousness. Once the applicant attempts rebuttal of a *prima facie* case of obviousness, the examiner must reweigh all the evidence anew. *Application of Lunsford*, 357 F.2d 385, 389-390; 148 USPQ 721, 724 (CCPA 1966).

4. SURPRISING RESULTS

Having presented argument that the *prima facie* case of obviousness was fully rebutted by evidence of the art being unpredictable, applicants now present evidence traversing the *prima facie* case of obviousness by presenting the same experimental evidence as both surprising and advantageous. Although the arguments are similar in subject matter, traversal of a

prima facie case of obviousness typically requires declaratory evidence evincing surprising advantages.

Two similar Rule 132 Declarations are presented here. One by inventor, Dr. Ronit Sagi-Eisenberg and one by an expert who is not a co-inventor, Dr. Ehud Razin. In the two declarations, the two scientists explain that the unpredictability of the two mast cell inhibitor peptides to inhibit mast cell secretion once fused to a CPP may be due to a variety of unpredictable factors. On page 5, the scientists explain that once CPP penetration has occurred, the biological effect of the mast cell inhibitor cargo peptide on the mast cell may be influenced because of:

- Conformation changes associated with the fusion;
- Degradation of the "foreign" peptide in the cell;
- Sequestering of the fusion peptide in an endosome; and
- Ability of the CPP to trigger mast cell release.

And as the scientific results clearly demonstrate, the scientists' considered position is born out. Of four CPP's tested, only one (KFGF) was suitable for delivery of the two mast cell inhibitor proteins. This was a *surprise* and an obvious *advantage* over the prior art depicting a universe of heretofore equivalent CPPs.

Lastly, the Examiner is reminded that she cannot simply pick and chose references that support her position. Just like the skilled artisan, the Examiner cannot ignore the totality of the prior art. The totality of prior art, going beyond Lin and including the other three CPPs, clearly does not focus on Lin's CPP being special while denigrating the penetrating ability of the other CPPs. Thus, we must assume, as the applicants did, that all reported CPPs would work to some degree to deliver mast cell inhibiting peptides, $G\alpha t$ or $G\alpha i_3$, in a functional form to mast cells. The fact that they are not equivalents is the underlying patentable feature of this invention and of the pending claims.

Having explained that the combination of Lin, Holgate and Aridor fails to set forth a *prima facie* case of obviousness, and/or that the *prima facie* case of obviousness is

traversed by presentation in the original specification of evidence of unpredictable, surprising and advantageous results, applicants request that the §103 rejection be withdrawn.

Holgate in view of Aridor and Lin and further in view of Avruch and Jackson.

Claims 64 and 65 are rejected under 35 U.S.C. §103(a) over Holgate in view of Aridor and Lin and further in view of Avruch and Jackson. Holgate, Aridor and Lin are relied upon as set forth above. Avruch describes the value of succinylation of the amino terminal ends of peptides to facilitate cell penetration, and Jackson teaches the value of cyclization of a peptide to stabilize confirmation. Claims 64 and 65 depend from claim 63, and applicants rely upon the above arguments for claim 63 to rebut and/ or traverse the *prima facie* case of obviousness.

Double Patenting

The pending claims are provisionally rejected on the grounds of double patenting over claims 1-44 of copending USSN 10/465,826 and claims 1-15 of copending USSN 11/214,588. No substantive response is deemed helpful at this time. According to the MPEP at page 804, a provisional double patenting rejection must be withdrawn in one of the applications when it is the sole remaining basis for rejection.

CONCLUSION

In view of the foregoing, applicants believe all claims now pending in this application are in condition for allowance, and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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Attachments: Petition to Extend Time (1 month)
Rule 132 Declarations of Dr. Ehud Razin and Dr. Ronit Sagi-Eisenberg

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